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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,817	SMITH ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,16,17,25,31-34,36-39,43,44,49 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 15, 18-21, 26-28, 30, 35 and 46-48 have been canceled. Claims 12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49 and 50 remain pending and under consideration in the instant application.

Applicant's arguments filed 2-13-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

The claims as originally filed specifically claimed using PD098059 in culturing ES cells, but did not specifically claim using U0126. The original election was to culturing ES cells in the presence of a compound that promotes propagation of ES cells and a compound that inhibits the ras/MAPK cascade (Group II). Applicants elected the species PD098059 as the compound that inhibits the ras/MAPK. Applicants' argued (10-23-02) that the mechanisms of action by which the second compound inhibited ES cell propagation varied (affecting SHP-2, ras/MAPK, MEK, mitogen activated protein kinase, or cyclin dependent entry into S-phase of non-ES cells). This argument was flawed and found not persuasive. The second compound inhibits non-ES propagation. Applicants stated the Groups share a "technical feature," but applicants did not disclose the "technical feature" or limit the claims to PD098059.

Applicants have amended claims 12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49 and 50 to culturing ES cells in the presence of a first compound that promotes propagation of ES cells and a second compound different than the first compound that is an inhibitor of MEK. Methods of culturing ES using inhibitors of MEK (Group III) is a non-elected Group. Apparently, applicants believe PD098059 inhibits the ras/MAPK cascade (Group II) and inhibits MEK (Group III). It is noted, however, that the specification does not confirm this and applicants have not provided any arguments that PD098059 inhibits the ras/MAPK cascade (Group II) and inhibits MEK. To expedite prosecution, the claims will be examined only as they relate to culturing ES cells using PD098059. Groups II and III have not been recombined. In this case, the use of PD098059 in culturing ES cells was patentably distinct from other compounds and the mechanism of action of PD098059 was not known. Therefore, the claims as originally filed did not properly set forth the Groups for examination.

To add to the confusion, claims 12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49 and 50 as newly amended are generic to using PD098059 or U0126. Methods of using PD098059 and U0126 would be patentably distinct because two methods require two different products having different structures that function by different modes of operation. The search for each method together would be undue. The method of culturing ES cells using PD098059 does not require the method of culturing ES cells using U0126. The method of culturing ES cells using U0126 does not require the method of culturing ES cells using PD098059. Therefore, applicants' original election of

using PD098059 in culturing ES stands. The claims will not be examined as they relate to methods of using U0126 to culture ES cells.

Limiting the claims to PD098059 as the second compound is suggested.

Priority

A certified copy of PCT/GB99/03031, filed on 9-13-99, now WO00/15764 is not required in the instant application because PCT/GB99/03031 is the international stage of the instant application. A certified copy of 9819912.8 filed in the United Kingdom on 9-11-98 was filed 3-9-01 (see the letter sent by the patent office April 12, 2001, which states a copy of the international application was filed). The courtesy copy filed 2-13-04 of the certified copy of priority document GB9819912.8 has been entered.

Drawings

The specification describes Figures 1-8 (pg 13, line 24), but no drawings are present in the application.

Claim Objections

In claim 37, step v) should refer to the dissociated cells from (iv), not (iii). See language used in claim 34, step (iv), which refers to dissociated cells from (iii).

The phrase "the MEK inhibitor" in claim 38 lacks literal antecedent basis in claim 37 and should be "the compound that inhibits MEK" to be more clear.

Limiting the claims to "a second compound that is different than the first compound, wherein the second compound is PD098059" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49 and 50 as newly amended are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12, 14, 16, 17 and 50 are being considered under new matter and written description as they relate to a method of culturing ES cells in the presence of a first compound that activates gp130 and promotes propagation of ES cells and a second compound different than the first that inhibits MEK and inhibits propagation of non-ES cells.

Claims 25 and 31-33 are being considered under new matter and written description as they relate to a culture medium for ES cells comprising a first compound that activates gp130 and a second compound different than the first that inhibits MEK.

Claims 34, 36, 39 and 49 are being considered under new matter and written description as they relate to a method of deriving ES cells using a first compound that activates gp130 and a second compound different than the first that inhibits MEK.

Claims 37 and 38 are being considered under new matter and written description as they relate to a method of deriving ES cells using a compound that inhibits MEK.

Claims 43 and 44 are being considered under new matter and written description as they relate to a method of culturing ES cells comprising expressing a compound that inhibits MEK.

Compounds that "activate gp130 and promote propagation of ES cells" (claim 12) do not have adequate written description. While the specification states such compounds include i) LIF and ii) the combination of IL-6 and IL-6 receptor (pg 8, lines 8-11; see also Nichols, Exp. Cell Research, 1994, Vol. 215, pg 237-239, regarding IL-6 and IL-6R), no other compounds are described or can be envisioned. LIF and the combination of IL-6 and IL-6 receptor do not share any structural features and have significantly different functions. Therefore, LIF and the combination of IL-6 and IL-6 receptor do not adequately represent the broad genus of compounds potentially encompassed by the phrase. An adequate written description of compounds having the ability to activate gp130 and promote propagation of ES cells requires more than a mere statement that the compounds are part of the invention and reference to a potential method for isolating such compounds; what is required is a description of the compounds themselves. It is not sufficient to merely refer to compounds having the ability to activate gp130 and to promote propagation of ES cells, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any compounds having those biological properties. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a

description of that material. Thus, claiming all compounds that achieve a result without defining the specific structures of a reasonable representation of such compounds is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, the phrase is new matter and lacks written description.

Compounds that "inhibit MEK and inhibit propagation of cells other than ES cells" (claim 12) do not have adequate written description. While the specification states PD098059 and U0126 inhibit MEK (pg 5, lines 27-31) and that the inhibitor of MEK may inhibit the cell cycle of differentiated cells, no compounds that inhibit MEK and inhibit propagation of any non-ES cell as broadly claimed are described. Specifically, PD098059 and U0126 do not inhibit propagation of any "cells other than ES cells" as broadly claimed. Even if PD098059 and U0126 do inhibit propagation of any non-ES cell, PD098059 and U0126 do not share any structural features and have function by significantly different mechanisms. Therefore, PD098059 and U0126 do not adequately represent the broad genus of compounds potentially encompassed by the phrase. An adequate written description of compounds having the ability to inhibit MEK and inhibit propagation of cells other than ES cells requires more than a mere statement that the compounds are part of the invention and reference to a potential method for isolating such compounds; what is required is a description of the compounds themselves. It is not sufficient to merely refer to compounds having the ability to inhibit MEK and inhibit propagation of cells other than ES cells, because disclosure of no more than that, as in

the instant case, is simply a wish to know the identity of any compounds having those biological properties. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all compounds that achieve a result without defining the specific structures of a reasonable representation of such compounds is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, the phrase is new matter and lacks written description.

The specification does not provide adequate written description for the "synergistic combination" of a first compound that activates gp130 and promoters propagation of ES cells and a second compound different than the first that inhibits MEK and inhibits propagation of non-ES cells (claim 12). The specification does not describe whether any combination of the two compounds is "synergistic" or whether only specific amounts of the two compounds in combination are "synergistic." An adequate written description of the "synergistic combination" of two compounds requires more than a mere statement that the "synergistic combination" is part of the invention and reference to a potential method for obtaining synergy; what is required is a description of the combinations compounds themselves and the amounts of such compounds required to obtain synergy. It is not sufficient to merely refer to "synergistic combinations" of compounds, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of compounds having synergy. Naming a combination of

compounds generically known to exist, in the absence of knowledge as to what combinations are synergistic, is not a description of that material. Thus, claiming all compound combinations that are synergistic without defining the specific structures of a reasonable representation of such compounds is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, "synergistic combinations" of the first and second compounds as newly amended are new matter and lack written description.

Compounds that "activate gp130" (claims 25, 34) do not have adequate written description. While the specification states such compounds include i) LIF and ii) the combination of IL-6 and IL-6 receptor (pg 8, lines 8-11; see also Nichols, Exp. Cell Research, 1994, Vol. 215, pg 237-239, regarding IL-6 and IL-6R), no other compounds are described or can be envisioned. LIF and the combination of IL-6 and IL-6 receptor do not share any structural features and have significantly different functions. Therefore, LIF and the combination of IL-6 and IL-6 receptor do not adequately represent the broad genus of compounds potentially encompassed by the phrase. An adequate written description of compounds having the ability to activate gp130 requires more than a mere statement that the compounds are part of the invention and reference to a potential method for isolating such compounds; what is required is a description of the compounds themselves. It is not sufficient to merely refer to compounds having the ability to activate gp130, because disclosure of no more than that, as in the instant

case, is simply a wish to know the identity of any compounds having those biological properties. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all compounds that achieve a result without defining the specific structures of a reasonable representation of such compounds is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, the phrase is new matter and lacks written description.

Compounds that "inhibit MEK" (claims 25, 34, 37) do not have adequate written description. While the specification states PD098059 and U0126 inhibit MEK (pg 5, lines 27-31) PD098059 and U0126 do not share any structural features and have function by significantly different mechanisms. Therefore, PD098059 and U0126 do not adequately represent the broad genus of compounds potentially encompassed by the phrase. An adequate written description of compounds having the ability to inhibit MEK requires more than a mere statement that the compounds are part of the invention and reference to a potential method for isolating such compounds; what is required is a description of the compounds themselves. It is not sufficient to merely refer to compounds having the ability to inhibit MEK, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any compounds having those biological properties. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that

material. Thus, claiming all compounds that achieve a result without defining the specific structures of a reasonable representation of such compounds is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, the phrase is new matter and lacks written description.

The limitations of "dissociating the cells" and "maintaining the dissociated cells" in claims 34 and 37 are new matter and lack written description. Applicants have not pointed to support for these new steps by page and line number and none can be found.

The limitation of developing an embryo in vitro (claim 37) is new matter. Applicants have not pointed to support for this new step by page and line number and none can be found.

The limitation of "expressing in ES cells a compound that inhibits MEK" in claim 43 does not have support in the specification as originally filed. Applicants have provided no support and none can be found. Nowhere does the specification describe a protein that inhibits MEK, a protein "expressed" by naturally that inhibits MEK or expressing a protein that inhibits MEK in a cell using a vector.

The limitation of a "MAP kinase phosphatase" being a compound that inhibits MEK (claim 44) is new matter. Applicants have provided no support and none can be found.

Claims 12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49 and 50 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 12, 14, 16, 17 and 50 are being considered under enablement as they relate to culturing ES cells in the presence of a first compound that activates gp130 and promotes propagation of ES cells and a second compound different than the first that is PD098059.

Claims 25 and 31-33 are being considered under enablement as they relate to a culture medium for ES cells comprising a first compound that activates gp130 and promotes propagation of ES cells and a second compound different than the first that is PD098059.

Claims 34, 36, 39 and 49 are being considered under enablement as they relate to a method of deriving ES cells using a first compound that activates gp130 and a second compound different than the first that is PD098059.

Claims 37 and 38 are being considered under enablement as they relate to a method of deriving ES cells using PD098059.

Claims 43 and 44 are being considered under enablement as they relate to a method of culturing ES cells comprising transfected with a vector encoding a compound that inhibits MEK.

The specification teaches D027 ES cells that are lif -/- and have an IRES-β-geo reporter gene inserted within the oct-4 gene locus. The structure or function of the "IRES-β-geo reporter gene inserted within the oct-4 gene locus" cannot be envisioned; it is unclear if the reporter protein is expressed under the control of the oct-4 promoter or if the IRES-β-geo reporter gene replaces the oct-4 gene. The specification teaches ZIN40 ES cells which express β-gal in differentiated cells. The structure or function of the ZIN40 cells cannot be determined; it is unclear if β-gal is expressed in all cells that undergo any amount of differentiation or only certain types of differentiation; it cannot be determined how to regulate expression of a protein so that it is expressed only upon differentiation. D027 cells were used in a self-renewal assay where PD098059 was added to the cells (pg 18, line 4-14). The results indicated PD098059 increased self-renewal at a concentration of 2-25 μM but not 50 μM (pg 23, lines 6-19). The specification states ES cells propagated in PD098059 remain pluripotent (pg 24, line 9); however, the statement is based on an experiment in which ZIN40 ES cells were treated with PD098059 with or without LIF. The specification teaches using IOUD2 ES cells, which carry a βgeo gene in the oct-4 locus. The structure and function of the IOUD2 ES cells cannot be determined; it is unclear if βgeo is expressed under the control of the oct-4 promoter or if the βgeo gene replaces the oct-4 gene. No correlation between the genetically altered ES described in the examples and normal ES cells is provided.

Overall, the claims are not enabled because the specification does not teach the starting material used in the assays described. All of the ES cells described in the

specification were genetically altered, which appears to be essential to the invention. But the vectors used to make the ES cells were not adequately taught in the specification. Without knowledge as to the structure and function of the genetically altered ES cells used in the assays, one of skill would not know how to repeat the results. The specification does not correlate the genetically altered ES cells to any other ES cells so that one of skill would expect the culture conditions used in the examples to cause the same effect in any other ES cells. The specification does not teach PD098059 inhibits propagation or survival of non-ES cells as claimed. It would require one of skill undue experimentation to determine how to perform the method described in the examples because the structure and function of the genetically altered ES cells is not taught. It would require one of skill undue experimentation to determine how to promote propagation/survival of ES cells and inhibit propagation of other cells as claimed using the teachings in the specification, specifically in the examples, because the specification does not correlate the results obtained in genetically altered ES cells of unknown structure and function to ES cells known in the art.

Applicants argue the constructs used to exemplify the methods of the invention were known in the art, e.g. US Patent 6,150,169. Applicants' argument is not persuasive. US Patent 6,150,169 was not available to the public until Nov. 20, 2000, about two years after the effective filing date of the instant application. Therefore, the public did not know the constructs described in 6,150,169 at the time of filing. One of skill would not have known the ES cells had a reporter gene under the control of the oct-4 promoter because the specification merely states the "IRES-β-geo reporter gene [was]

inserted within the oct-4 gene locus". It cannot be determine where the reporter gene was inserted into the oct-4 gene or whether the oct-4 gene locus was deleted before inserting the reporter gene. Pg 21, lines 30-32, does not teach β-gal expression was limited to ES cells or that the β-gal gene was operably linked to the oct-4 promoter.

Applicants point to Mountford (1995, TIG, Vol. 11, pg 1179-184) and state the reference describes how to make IRES-containing constructs used in the invention (pg 9 of response, 2nd ¶). Applicants' argument is not persuasive. Nowhere does Mountford teach the promoter of the endogenous gene must be kept. Nowhere does the specification limit the methods of constructing the ES to the teachings of Mountford. In addition, Mountford taught different vectors having different structures (Fig. 2, pg 181), different applications (Figs. 3 and 4, pg 183). One of skill would not have been able to guess which vector or application was used in the ES cells described in the specification as originally filed.

Applicants argue pg 182, right column, confirms ZIN40 is an ES cell line. Applicants' argument is not persuasive. The last two sentences of the second full paragraph merely state "[s]everal nuclear-localized fusions have been isolated with this vector. One of these, ZIN40, gives strong and apparently ubiquitous nuclear expression of β-galactosidase in embryonic and adult mouse tissues." No mention of ZIN40 as being an ES cell line can be found.

Applicants argue pg 23, lines 13-15, taught PD098059 increased self-renewal of ES cells and pg 26, lines 24-26, taught PD098059 increased the number ES cells. Therefore, applicants conclude the specification enables the claims. Applicants'

argument is not persuasive because pg 23 required D027 cells and IOUD2 ES cells. D027 and IOUD2 ES cells were genetically altered, but the specification does not provide adequate guidance for one of skill to determine the structure of those cells. Applicants have not provided any evidence that PD098059 functions as claimed in non-transfected ES cells.

Applicants provide Williams (June 1998, Biochem., Vol. 37, pg 9579-9785) and state Williams taught an MEK inhibitor that was available at the time of filing. While Williams taught Ro 09-2210 inhibited MEK1, it is not readily apparent that Ro 09-2210 inhibited ES cell propagation as claimed or that inhibition of MEK1 alone was adequate to inhibit ES cell propagation. Applicants do not teach the amount of inhibition of MEK1 obtained with Ro 09-2210 is the same as the amount of inhibition of MEK1 obtained with PD098059 or U0126.

Applicants argue contribution of ZIN40 ES cells to chimeras was disclosed on pg 19, lines 26-28, and confirmed on pg 24, lines 20-22. Applicants' argument is not persuasive. The embryos were sacrificed on day 9.5 of pregnancy (pg 19, line 27). Mid-gestation mouse embryos are not chimeric mice because they have not been born.

Claims 12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49 and 50 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of compounds that "activate gp130 and promote propagation of ES cells" other than LIF and the combination of IL-6 and IL-6R cannot be

determined (claim 12). LIF and the combination of IL-6 and IL-6R do not share the same structure and have significantly different functions. Others in the genus cannot be envisioned. Therefore, the metes and bounds of the compounds cannot be determined.

The metes and bounds of a compound that is "an inhibitor of MEK and inhibits propagation of cells other than ES cells" other than PD098059 and U0126 cannot be determined (claim 12). PD098059 and U0126 have different structures and have significantly different functions. Others in the genus cannot be envisioned. Therefore, the metes and bounds of the compounds cannot be determined.

It is unclear if the phrase "wherein the first compound is a cytokine that activates gp130 in ES cells" (claims 16 and 32) is merely attempting to limit the type of compound to a cytokine or if the phrase is limiting the type of compound to a cytokine and to activating gp130 in the ES cells. If applicants are merely attempting to limit the first compound to a cytokine, please delete the phrase "that activates gp130 in ES cells." For example, it is unclear if the "ES cells" in claim 16 refer specifically to the ES cells in culture in claim 12 or if the "ES cells" in claim 16 are generic to any ES cells.

The metes and bounds of compounds that "activate gp130" other than LIF and the combination of IL-6 and IL-6R cannot be determined (claim 25, 34). LIF and the combination of IL-6 and IL-6R do not share the same structure and have significantly different functions. Others in the genus cannot be envisioned. Therefore, the metes and bounds of the compounds cannot be determined.

The metes and bounds of a compound that is "an inhibitor of MEK" other than PD098059 and U0126 cannot be determined (claim 25, 34, 37). PD098059 and U0126

have different structures and have significantly different functions. Others in the genus cannot be envisioned. Therefore, the metes and bounds of the compounds cannot be determined.

The term "MAP kinase phosphatase" in claim 44 does not further limit a "compound that inhibits MEK" as in claim 43. Nowhere does the specification teach that MAP kinase phosphatase inhibits MEK. Only PD098059 and U0126 are described as inhibiting MEK.

The phrase "the compound that selectively inhibits" (claim 49) lacks antecedent basis in claim 34. Delete "selectively" to overcome this rejection.

The metes and bounds of the method of culturing ES cells (claim 34, 37, 43) cannot be determined.

It is unclear if genetic alteration is encompassed by claim 43, and if so, is the cell genetically altered to express PG098059? Applicants point to Example 3 (pg 27, lines 25-32). Applicants' argument is not persuasive. Example 3 describes transfecting ES cells with a vector encoding MKP-3; however, the specification does not teach MKP-3 inhibits MEK as claimed. It cannot be determined which mode of action caused reduced differentiation of ES cell as compared to non-transfected cells. If applicants intended claims 43 and 44 to be limited to a cell comprising a vector encoding MKP-3 or some other protein, such claims would have been restricted away from the other claims under consideration because transfected cells have a different structure and function than cells cultured in the presence of two different compounds.

Claim Rejections - 35 USC § 102

Claims 12, 14, 16, 17 and 50 are being considered under 102 and 103 as they relate to a method of culturing ES cells in the presence of a first compound that activates gp130 and promotes propagation of ES cells and a second compound different than the first that is PD098059.

Claims 25 and 31-33 are being considered under 102 and 103 as they relate to a culture medium for ES cells comprising a first compound that activates gp130 and promotes propagation of ES cells and a second compound different than the first that is PD098059.

Claims 34, 36, 39 and 49 are being considered under 102 and 103 as they relate to a method of deriving ES cells using a first compound that activates gp130 and promotes propagation of ES cells and a second compound different than the first that is PD098059.

Claims 37 and 38 are being considered under 102 and 103 as they relate to a method of deriving ES cells using PD098059.

Claims 43 and 44 are being considered under 102 and 103 as they relate to a method of culturing ES cells comprising expressing a compound that inhibits MEK.

Claims 12, 14, 16, 17, 25, 31-33, 43, 44 and 50 remain rejected under 35 U.S.C. 102(a) as being anticipated by Niwa of record (July 1, 1998, Genes & Development, Vol. 12, pg 2048-2060). Claims 34, 36-39 and 49 have been withdrawn

from the rejection because Niwa did not teach "dissociating" the cells or "maintaining" the dissociated cells as newly claimed.

Niwa taught PD098059 blocked activation of the ERK kinases but does not inhibit ES cell colony formation in response to LIF (pg 2056, col. 1, 7 lines from the bottom). Thus, Niwa cultured ES cells in LIF and PD098059, which inherently has all the effects, claimed. LIF is the first compound and PD098059 is the second compound as claimed.

Applicants argue Niwa is not "work by another" because it was performed at the direction of inventors Tom Burdon and Austin Smith. Applicants' argument is not persuasive. Such a statement must be in the form of a declaration by Tom Burdon and Austin Smith to be persuasive (see MPEP 715.01(c) and 716.10 regarding a reference that is a publication of Applicant's own invention).

Applicants argue Niwa does not anticipate the claims because Niwa taught PD098059 did not teach inhibit stem cell growth. Applicants' argument is not complete because it does not relate to the claims. The claims require an inhibitor of MEK that inhibits propagation of cells other than ES cells. PD098059 is such a compound. PD098059 inherently inhibited propagation of non-ES cells in the method taught by Niwa.

Applicants argue Niwa did not teach a synergy between LIF and PD098059 promoted propagation of ES cells. Applicants' argument is not persuasive. Niwa did not have to teach the synergy between LIF and PD098069 because Niwa taught culturing ES cells with LIF and PD098059. The method taught by Niwa implicitly and

inherently resulted in synergy because both compounds required to obtain synergy were used in the culture method.

Applicants' argument bridging pg 12-13 of the response filed 2-13-04 cannot be discerned. Applicants discuss the teachings in the specification, but do not correlate the teachings to the claims or correlate the claims to Niwa. Applicants do not specifically set forth the limitations in claims 25 and 31-33 that are not taught by Niwa. Therefore, applicants' argument is not persuasive because Niwa taught culturing ES cells with LIF and PD.

Applicants' arguments regarding claims 34, 36-39 and 49 are persuasive (pg 13 of response filed 2-13-04, 3rd and 4th full ¶) because Niwa did not teach maintaining the ES cells and dissociating the cells followed by maintaining the dissociated cells with a compound that activated gp130 and a different compound that inhibits MEK. Claims 34, 36-39 and 49 have been withdrawn from the rejection.

Applicants' argue Niwa did not express a transgene; therefore, applicants conclude that Niwa did not anticipate claims 43 and 44. Applicants' argument is not persuasive because claims 43 and 44 do not require a transgene.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

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